74 can be found, for example, on page 6, lines 1-10, Figure 2, and on page 16, lines 10-17. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

The present invention is directed to an enhanced LM609 grafted antibody exhibiting selective binding affinity to $\alpha_v\beta_3$, or a functional fragment thereof, comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, the antibody or functional fragment thereof having integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity, wherein the $\alpha_v\beta_3$ binding affinity of the enhanced LM609 grafted antibody is maintained. The invention also provides enhanced LM609 grafted antibodies having CDRs referenced as specific SEQ ID NOS as well as high affinity LM609 grafted antibodies. Applicant respectfully traverses all grounds for rejecting the claims for the reasons that follow.

Regarding Priority

Applicant herewith has amended the specification to delete the claim to priority under 35 U.S.C. § 120, which indicated that the above-identified application is a continuation-in-part of U.S. Application 08/791,391, filed January 30, 1997. Accordingly, Applicant hereby disclaims priority to any earlier applications. Therefore, the priority date of the subject application is the actual filing date, January 30, 1998.

Regarding Inventorship

The above-identified application has been amended during prosecution to cancel claims so that fewer than all of the currently named inventors are the actual inventors of the invention being claimed in the application. A change of inventorship under 37 C.F.R. § 1.48(b) to delete Scott M. Glaser as an inventor is respectfully requested. As required by § 1.48(b), attached herewith is a petition including a statement identifying each named inventor who is being deleted, namely Scott M. Glaser, and acknowledging that the inventor's invention is no longer being claimed in the application. The petition also includes the required fee under 37 C.F.R. § 1.17(i).

Regarding Election of Claims in Response to Restriction Requirement

The Office Action acknowledges the election of Group I, claims 56-97, for examination. The Office Action indicates that the election has been treated without traverse because Applicant allegedly did not distinctly and specifically point out the supposed error in the restriction requirement.

Applicant respectfully submits that the election of Group I was made with traverse in the response filed September 8, 1999, to the original restriction requirement mailed April 8, 1999. In the response filed September 8, 1999, Applicant canceled claims 1-55, elected the remaining claims of Group I, claims 58-79, and argued that new claims 80-104, which parallel the method claims restricted into Group II, would not be an undue burden to examine together with the claims of Group I. The

second restriction requirement mailed November 24, 1999, acknowledges the traversal made in the previous response as it applied to the currently pending claims (section 4, third paragraph). The restriction requirement mailed November 24, 1999, further required the election of a species of antibody. In Applicant's response mailed April 24, 2000, Applicant reiterated the election of Group I and elected a species for examination. However, Applicant did not reiterate the traversal since the Office Action mailed November 24, 1999, appeared to acknowledge the previous traversal.

Applicant respectfully submits that, in contrast to the indication in the Office Action mailed July 18, 2000, Applicant did elect Group I with traverse.

Rejections Under 35 U.S.C. § 112

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 stand rejected under 35 U.S.C. § 112, first paragraph. The Office Action indicates that the LM609 antibody is required to practice the claimed invention.

Applicant submits that the specification provides sufficient description and guidance so as to enable those skilled in the art to practice the invention as claimed. The nucleotide sequence and deduced amino acid sequence of LM609 heavy chain variable region (SEQ ID NOS: 5 and 6, respectively) and LM609 light chain variable region (SEQ ID NOS:7 and 8, respectively) are disclosed in the specification (see Figure 2 and page 6, lines 1-10). Using the disclosed nucleotide sequences of the LM609 heavy and light chain variable regions, which provide

antibody specificity, one skilled in the art can readily obtain an LM609 antibody or functional fragment thereof using methods well known in the art. Thus, the disclosure of the nucleotide sequence of the LM609 heavy and light chain variable regions is all that is necessary to practice the invention as claimed. Therefore, the rejection of claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 is respectfully requested to be withdrawn.

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 stand rejected under 35 U.S.C. § 112, first and second paragraphs, as allegedly lacking enablement. The claims are indicated to be indefinite for the terms "enhanced LM609 grafted antibody" and "functional fragment thereof" because their characteristics are allegedly not known. The Office Action indicates that it is not clear from the disclosure which particular "enhanced" or "function" is being referred to.

Applicant respectfully submits that "enhanced LM609 grafted antibody" and "functional fragment thereof" are clear and definite and that the specification provides sufficient description and guidance to enable the claimed invention. In regard to the term "enhanced," the specification teaches that an enhanced antibody is one in which a functional characteristic of the antibody has been altered or augmented compared to a reference antibody so that the antibody exhibits a desirable property or activity (see page 16, line 30, to page 17, line 14). Exemplary enhanced activity includes higher or lower affinity, increased or decreased association or dissociation rates, or increased stability compared to a reference antibody such as the LM609 grafted parent antibody (page 17, lines 3-14). Furthermore, claim 56 specifically recites that the $\alpha_v\beta_3$ binding

activity of the enhanced LM609 grafted antibody is maintained, and claim 74 specifically recites that the $\alpha_v\beta_3$ binding activity of the high affinity LM609 grafted antibody is enhanced. Therefore, Applicant respectfully submits that the claims recite specific functional characteristics of the claimed enhanced antibodies.

In regard to the term "functional fragment," the specification teaches that a functional fragment, when used in reference to a LM609 grafted antibody or to heavy or light chain polypeptides thereof, refers to a portion which still retains some or all of the $\alpha_v\beta_3$ binding activity, $\alpha_v\beta_3$ binding specificity, and/or integrin $\alpha_v\beta_3$-inhibitory activity (see page 16, lines 10-29). Furthermore, claims 56 and 74, as amended, recite specific functional characteristics of the claimed enhanced antibodies, that the antibody or functional fragment thereof has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity. Moreover, the claims recite specific structural characteristics of the claimed enhanced antibodies comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8.

Applicant respectfully disagrees with the assertion on page 4, paragraph 2, that the claims broadly encompass a significant number of inoperative species. The claims, as amended, specifically recite functional characteristics of the claimed enhanced antibodies. In particular, claims 56 and 74 recite that the antibody or functional fragment thereof has

integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity and that the $\alpha_v\beta_3$ binding affinity of the enhanced LM609 grafted antibody is maintained or enhanced, respectively. Therefore, Applicant respectfully submits that the claims are directed to operative embodiments having specifically recited functional characteristics.

Applicant submits that the claims are clear and definite and that the specification provides sufficient description and guidance to enable the claimed invention. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the term "LM609." The Office Action indicates that LM609 is a laboratory designation which does not clearly define the claimed product since different laboratories may use the same laboratory designation to define completely distinct cell lines or hybridomas. Applicant respectfully submits that the claims are clear and definite. Claims 1 and 74, as amended, recite specific SEQ ID NOS for the LM609 grafted heavy chain variable region polypeptide and LM609 grafted light chain variable region polypeptide. Therefore, Applicant respectfully submits that the claims recite specific structural features of the claimed enhanced LM609 grafted antibody and are clear and definite. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 56-59, 62, 65-68, 70-75, 77, 84, 85, 90, 91 and 94-97 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Brooks et al., U.S. Patent No. 5,753,230. The Office Action indicates that Brooks et al. describes the LM609 antibody as well as humanized forms of this antibody. The Office Action indicates that the claimed "enhanced LM609 antibody" can have contrasting properties, that is, altered or augmented compared to a reference antibody, and still be considered enhanced with respect to the reference LM609 antibody. The Office Action concludes that, given the prior art description of humanized LM609 antibodies and the claimed recitation of "enhanced LM609 antibody," which allegedly encompasses a variety of modified forms of LM609, the prior art humanized antibodies read on the claimed antibodies.

Applicant respectfully submits that the claimed enhanced antibodies are novel over Brooks et al. Claim 56, as amended, is directed to an enhanced LM609 grafted antibody exhibiting selective binding affinity to $\alpha_v\beta_3$, or a functional fragment thereof, comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, where the antibody or functional fragment thereof has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity and where the $\alpha_v\beta_3$ binding affinity of the enhanced LM609 grafted antibody is maintained. Claim 74, as amended, is directed to a high affinity LM609 grafted antibody exhibiting selective binding

affinity to $\alpha_v\beta_3$, or a functional fragment thereof, comprising at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, where the antibody or functional fragment thereof has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity or integrin $\alpha_v\beta_3$-inhibitory activity and where the $\alpha_v\beta_3$ binding affinity of the high affinity LM609 grafted antibody is enhanced.

In contrast to the claimed enhanced antibodies, Brooks et al. does not teach an enhanced LM609 grafted antibody comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8. Absent such a teaching, Brooks et al. cannot anticipate the claimed invention. Accordingly, Applicant respectfully submits that the claimed enhanced LM609 grafted antibodies are novel over Brooks et al. and requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 56-59, 62, 66-68, 70, 71, and 74-76 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Brooks et al., U.S. Patent No. 5,753,230, in view of known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof. Applicant respectfully submits that the claimed enhanced LM609 grafted antibodies are unobvious over Brooks et al., alone or in view of known methods of gene cloning

and expression strategies. In contrast to the claimed enhanced LM609 grafted antibodies, Brooks et al. does not teach or suggest an enhanced LM609 grafted antibody comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8. Furthermore, any known art for gene cloning and expression strategies does not cure the deficiencies of Brooks et al. Accordingly, Applicant respectfully submits that the claimed enhanced LM609 grafted antibodies are unobvious over Brooks et al., alone or in combination with known methods for gene cloning and expression strategies, and requests that this rejection be withdrawn.

Regarding Claims Indicated to be Free of the Prior Art

In the Office Action on page 8, section 13, claims 65, 72, 73, 77, 84, 85, 90, 91, 94-97, which recite SEQ ID NOS:90 and 94, are indicated to be free of the prior art, as the prior art does not appear to suggest these particular CDRs for LM609-specific recombinant antibodies. Applicant respectfully points out that claim 62 also specifically recites SEQ ID NO:94 and, accordingly, should be considered free of the prior art as with the other indicated claims.

Provisional Double Patenting Rejection

Claims 56-59, 62, 65-68, 70-77, 84, 85, 90, 91 and 94-97 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-18 and 26-31 of copending application

serial No. 08/790,540 and claims 1-8, 15-26 and 33-42 of copending application serial No. 08/791,391. The Office Action indicates that, although the conflicting claims are not identical, they are not patentably distinct from each other because each application is drawn to the same or nearly the same LM609-specific antibodies and nucleic acids encoding the antibodies and modifications thereof.

Applicant respectfully submits that the claimed enhanced LM609 grafted antibodies are patentably distinct from the claims in either of copending application serial Nos. 08/790,540 or 08/791,391. The claims in either of application serial Nos. 08/790,540 or 08/791,391 are not directed to an enhanced LM609 grafted antibody comprising one or more CDRs having at least one amino acid substitution in one or more CDRs of a LM609 grafted heavy chain variable region polypeptide referenced as SEQ ID NO:6 or a LM609 grafted light chain variable region polypeptide referenced as SEQ ID NO:8, as claimed in the subject application. Accordingly, Applicant respectfully requests that the provisional double patenting rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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Date

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